

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-205

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

ITEM 13

PATENT INFORMATION

for

NDA 21-205

TRIZIVIR™ (abacavir sulfate/lamivudine/zidovudine) Tablets

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Trizivir™ Tablets
Active Ingredient:	abacavir sulfate, lamivudine, zidovudine
Strength(s):	300 mg abacavir sulfate 150 mg lamivudine 300 mg zidovudine
Dosage Form:	Tablet
sNDA Number:	21-205

Applicable Patent Numbers and Expiration Dates:

Patent No.	5,034,394
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Drug Drug Product

Patent No.	5,089,500
Expires:	June 26, 2009
Owner:	Glaxo Wellcome Inc.
Type:	Method of Use

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Patent No. 5,047,407
Expires: November 17, 2009
Owner: BioChem Pharma
(IAF BioChem International, Inc.)
license owned by Glaxo Wellcome Inc.

Type: Drug
Drug Product
Method of Use

Patent No. 5,905,082
Expires: May 18, 2016
Owner: Glaxo Group Ltd.
Type: Drug product
Method of Use

Patent No. 4,724,232
Expires: September 17, 2005
Owner: Glaxo Wellcome Inc.
Type: Drug Product
Method of Use

Patent No. 4,818,538
Expires: September 17, 2005
Owner: Glaxo Wellcome Inc.
Type: Drug Product

Patent No. 4,833,130
Expires: September 17, 2005
Owner: Glaxo Wellcome Inc.
Type: Method of Use

Patent No. 4,837,208
Expires: September 17, 2005
Owner: Glaxo Wellcome Inc.
Type: Method of Use

Patent No. 4,828,838
Expires: September 17, 2005
Owner: Glaxo Wellcome Inc.
Type: Drug Product

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Item 13
NDA 21-205
Page 3

The undersigned declares that U.S. Patent Nos. 5,034,394 and 5,089,500 cover the composition, formulation, and methods of use of TRIZIVIR™ (abacavir sulfate/lamivudine/zidovudine) Tablets. These U.S. patents should be included in Item 13 of NDA 21-205.

The undersigned declares that U.S. Patent Nos. 5,047,407 and 5,905,082 cover the composition, formulation, and methods of use of TRIZIVIR™ (abacavir sulfate/lamivudine/zidovudine) Tablets. These U.S. patents should be included in Item 13 of NDA 21-205.

The undersigned declares that U.S. Patent Nos. 4,724,232; 4,818,538; 4,833,130; 4,837,208; and 4,828,838 cover the composition, formulation, and methods of use of TRIZIVIR™ (abacavir sulfate/lamivudine/zidovudine) Tablets. These U.S. patents should be included in Item 13 of NDA 21-205.

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709
(919)483-2723

December 1, 1999
Date

Karen L. Prus
Karen L. Prus, Ph.D.
Registered Patent Attorney
Registration No. 39,337

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Exclusivity Checklist

NDA: 21-205

Trade Name: Trizivir™

Generic Name: (abacavir sulfate/lamivudine/zidovudine)

Applicant Name: Glaxo Wellcome Inc.

Division: HFD -530

Approval Date If Known: June 9, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a. Is it an original NDA? YES /X/ NO /__/

b. Is it an effectiveness supplement? YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.): NA

- c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /__/ NO /X/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation: The applicant submitted Protocol AZL10001: An Evaluation of the Bioequivalence of a Combined Formulated Tablet compared to each of the commercially available Tablets Administered in Healthy Volunteers to support approval of this application. No clinical data was submitted for review.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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d. Did the applicant request exclusivity?

YES / /

NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES / /

NO / /

If yes, NDA #
Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? YES / /

NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

YES / /

NO / /

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / /

NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product
NDA#

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2. Combination product

YES / X /

NO / /

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / X /

NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product: Ziagen (abacavir sulfate) Tablets
NDA# 20-977

Drug Product: Epivir (lamivudine) Tablets
NDA# 20-564

Drug Product: Retrovir (zidovudine) Tablets
NDA# 20-518

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?

(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / /

NO / X /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / ☐ /

/ NO / ☐ /

b. If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ☒ /

NO / ☐ /

1. If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ☐ /

NO / ☐ /

If yes, explain:

2. If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / ☐ /

NO / ☐ /

If yes, explain:

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- c. If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1:

YES / ☐ /

NO / ☐ /

Investigation #2:

YES / ☐ /

NO / ☐ /

Investigation #3:

YES / ☐ /

NO / ☐ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1—NDA Number:

Investigation #2—NDA Number:

Investigation #3—NDA Number:

- b. For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1:

YES / ☐ /

NO / ☐ /

Investigation #2:

YES / ☐ /

NO / ☐ /

Investigation #3:

YES / ☐ /

NO / ☐ /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #1—NDA Number:

Investigation #2—NDA Number:

Investigation #3—NDA Number:

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If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1:

Investigation #2:

Investigation #3:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES / ☐ /

NO / ☐ /

IND#

Explain:

Investigation #2

YES / ☐ /

NO / ☐ /

IND#

Explain:

Investigation #3

YES / ☐ /

NO / ☐ /

IND#

Explain:

- b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / ☐ /

NO / ☐ /

IND#

Explain:

Investigation #2

YES / ☐ /

NO / ☐ /

IND#

Explain:

Investigation #3

YES / ☐ /

NO / ☐ /

IND#

Explain:

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- c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/

NO /___/

If yes, explain:

Signature of PM/CSO:

Date:

5 - 30 - 00

1/31

Signature of Division Director:

Date:

6/8/00

1/31

cc:

Original NDA 21-205

Division File

HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21205 Trade Name: TRIZIVIR (ABACAVIR SULFATE/LAMIVUDINE/ZI
Supplement Number: Generic Name: ABACAVIR SULFATE/LAMIVUDINE/ZIDOVUDINE 3
Supplement Type: Dosage Form: TAB
Regulatory Action: PN Proposed Indication: Trizivir is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

 Neonates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy Adequate for ALL pediatric age groups

Formulation Status

Studies Needed

Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO**COMMENTS:**

Age groups 0 to 12 years (patients weighing less than 40kg) have been waived. Trizivir will be labeled for use in adolescents and adults who weigh more than 40 kg. These dosing recommendations are based on historical data with the individual components. Pediatric data were not submitted with the NDA. A PPSR dated May 4, 2000 was submitted by the sponsor. An IA letter will be issued in response to this proposed pediatric study request because additional labeling for pediatric dosing are not required under the 98 Pediatric Rule. 5/22/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
MELISSA TRUFFA

Signature

Date

5-30-00

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[FDA Links](#) [Tracking Links](#) [Check Lists](#) [Searches](#) [Reports](#) [Help](#)PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) [View Word Document](#)

NDA Number: 021205 Trade Name: TRIZIVIR (ABACAVIR SULFATE/LAMIVUDINE/ZI
Supplement Number: 000 Generic Name: ABACAVIR SULFATE/LAMIVUDINE/ZIDOVIDINE 3
Supplement Type: N Dosage Form:
Regulatory Action: AE COMIS Indication: TREATMENT OF HIV INFECTION
Action Date: 6/9/00

Indication # 1 Trizivir is indicated alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Label Adequacy: Adequate for SOME pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Age groups 0 to 12 years (patients weighing less than 40kg) have been waived. Trizivir will be labeled for use in adolescents who weigh more than 40 kg. These dosing recommendations are based on historical data with the individual components. Pediatric data were not submitted with the NDA. An Inadequate letter (IA) was issued to the sponsor on June 19, 2000 in response to the PPSR. A PPSR dated May 4, 2000 was submitted by the sponsor. An IA letter will be issued in response to this proposed pediatric study request because additional labeling for pediatric dosing are not required under the 98 Pediatric Rule. 5/22/00

Lower Range	Upper Range	Status	Date
-------------	-------------	--------	------

0 months	12 years	Waived	
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Comments: This is fixed dose combination product. Pediatric formulations of the three components of this fixed-dose tablet are available for use in patients 0-12 years of age.

12 years	16 years	Completed	
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This page was last edited on 11/20/00

Signature

Date

11-9-00


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New Drug Application

NDA 21-205; TRIZIVIR™
(abacavir sulfate/lamivudine/zidovudine)
Tablets

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller
Head, Clinical Compliance
World Wide Compliance

19 Nov 1989

Date

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GlaxoWellcome

December 10, 1999

Bank Mellon, N/A
Bank @ FDA
Food and Drug Administration
27th Floor (FDA 360909)
Three Mellon Bank Center
Pittsburgh, PA 15259-0001

Re: NDA 21-205; Trizivir™ (abacavir sulfate/lamivudine/zidovudine) Tablets
User Fee: Without Clinical Data

Please find enclosed Glaxo Wellcome check number 0002977 in the amount of \$136,141.00. This initial payment is 100% of the application fee for the New Drug Application that is being filed with the Center for Drug Evaluation and Research, FDA, Division of Antiviral Drug Products. Please note the User Fee ID Number for this submission is 3866.

Please find below requested information regarding this application.

Type of Application:	New Drug Application with Clinical Data	
	New Drug Application without Clinical Data	X
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-9347. Thank you.

Sincerely,



Martha Anne A. Moore, R.Ph.
Antiviral Group – Regulatory Affairs

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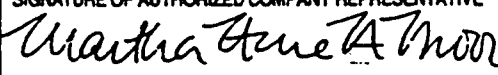
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Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0297 Expiration Date: 04-30-01
USER FEE COVER SHEET		
<i>See Instructions on Reverse Side Before Completing This Form.</i>		
1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709	3. PRODUCT NAME Trizivir™ (abacavir sulfate/lamivudine/zidovudine) Tablets	
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <i>No</i> IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).	
5. USER FEE I.D. NUMBER 3866	6. LICENSE NUMBER / NDA NUMBER NDA 21-205	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.		
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 <i>(Self Explanatory)</i> </div> <div style="width: 50%;"> <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. <i>(See item 7, reverse side before checking box.)</i> </div> </div> <div style="display: flex; flex-wrap: wrap; margin-top: 10px;"> <div style="width: 50%;"> <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i> </div> <div style="width: 50%;"> <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i> </div> </div> <div style="text-align: center; margin-top: 10px;"> <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY <i>(Self Explanatory)</i> </div> <p style="text-align: center; margin-top: 5px;">FOR BIOLOGICAL PRODUCTS ONLY</p> <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION </div> <div style="width: 50%;"> <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT </div> <div style="width: 50%;"> <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY </div> <div style="width: 50%;"> <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE FHS ACT </div> <div style="width: 50%;"> <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92 </div> </div>		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <div style="float: right;"> <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <i>(See reverse side if answered YES)</i> </div>		
<i>A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.</i>		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0297) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Martha Anne A. Moore	TITLE Antiviral Group, Regulatory Affairs	DATE December 10, 1999

FORM FDA 3397 (5/98)

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FOOD AND DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH, PA 15259

GlaxoWellcome

P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

DATE
12/10/99
RTPT

CHECK NO.
0002977
010340 PA

DATE	INVOICE/CREDIT MEMO	TYPE	DESCRIPTION	GROSS	DISCOUNT	NET
12/01/99	NDA21205			136141.00		136141.00
TOTAL				136141.00		136141.00

VERIFY THE AUTHENTICITY OF THIS MULTI-TONE SECURITY DOCUMENT. CHECK BACKGROUND AREA CHANGES COLOR GRADUALLY FROM TOP TO BOTTOM.

GlaxoWellcome

P.O. BOX 13358
RESEARCH TRIANGLE PARK, N.C. 27709

Wachovia Bank & Trust Company, N.A.
Asheville, N.C.

CHECK DATE
12/10/1999

CHECK NUMBER
0002977

CHECK VOID AFTER 120 DAYS

PAY TO THE ORDER OF **136141.00**

****\$136,141.00

ONE HUNDRED THIRTY SIX THOUSAND ONE HUNDRED FORTY ONE DOLLARS AND 00 CENTS

Pay to the order
FOOD AND DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH, PA 15259

Michael A. Johnson
Authorized Signature

0002977 053100355010459 002194

THE ORIGINAL DOCUMENT HAS A WHITE REFLECTIVE WATERMARK ON THE BACK. HOLD AT AN ANGLE TO SEE THE MARK WHEN CHECKING ENDORSEMENTS

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FINANCIAL DISCLOSURE AS TO CLINICAL INVESTIGATORS

Trizivir (abacavir sulfate/lamivudine/zidovudine)

NDA 21-205: Trizivir (abacavir sulfate/lamivudine/zidovudine) Tablets Original New Drug Application

In compliance with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 FR 5233), as subsequently revised by publication on December 31, 1998 (63 FR 72171) (hereafter collectively referred to as the "rule"), financial interest information is provided for clinical investigators participating in studies covered by the rule included in New Drug Application 21-205 for Trizivir (abacavir sulfate/lamivudine/zidovudine) for the treatment of Human Immunodeficiency Virus (HIV).

The following synopsis includes a description of methods used for the collection and reporting of the investigator financial disclosure information. Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and supporting tables can be found in Item 19 (Vol. 8 Page 238).

The following is the "covered clinical study" for purposes of the rule for which Glaxo Wellcome was the sponsor:

PROTOCOL NO.	PROTOCOL TITLE	STUDY START DATE	STOP DATE
AZL10001	An Evaluation of the Bioequivalence of a Combined Formulated Tablet (300/150/300mg abacavir/lamivudine/zidovudine) Compared to ZIAGEN (abacavir) 300mg tablet, EPIVIR (lamivudine) 150mg tablet, and RETROVIR (zidovudine) 300mg tablet Administered Concurrently and the Effect of Food on Absorption in Subjects with HIV-1 Infection	01 APR 99	01 AUG 99

Note: To arrive at the above-noted study "start" and "stop" dates, Glaxo Wellcome has defined the duration of the clinical study as the time period beginning with the first patient entered into the clinical study until the last patient assessment at the last site.

The rule specifies four categories of potentially disclosable financial interests. The approach taken to each is addressed below.

- Compensation potentially affected by the outcome of the covered study (21 CFR 54.4(a)(3)(i), 54.2(a))

Glaxo Wellcome does not compensate clinical investigators in such a way as the total amount could vary with the outcome of the study. This is now formally stated in an organization-wide policy statement. Consequently, there are no disclosures in this category.

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- **Significant payments of other sorts from the sponsor of the covered study (21 CFR 54.4(a)(3)(ii), 54.2(f))**

Glaxo Wellcome relied upon financial data available internally to determine if the \$25,000 threshold was exceeded in the case of any individual clinical investigator. Consistent with the December 31, 1998 revisions to the rule, only payments made on or after February 2, 1999 were tracked. In addition, Glaxo Wellcome imposed a US cut-off date of October 17, 1999 and Rest of World (RoW) payment cut-off date of August 31, 1999 to allow sufficient time (roughly 90 days in advance of the submission date) for "other" payment information to be extracted from financial systems, compiled, and otherwise made "application-ready". Glaxo Wellcome has treated reimbursements of out-of-pocket expenses (such as travel costs incurred in the course of performing compensated services) as outside the definition of "payments of other sorts."

Based on available financial data, the \$25,000 threshold for "payments of other sorts" (between February 2, 1999 and the above referenced cut-off dates) was not exceeded by any investigator participating in the study.

It is not Glaxo Wellcome's practice to seek, or to maintain on file, the names of clinical investigators' spouses and dependent children, which would be necessary were searches to be conducted for "other" payments relative to those names. In this regard, please be advised that Glaxo Wellcome will not agree to compensate clinical investigators by making payments to their spouses or dependent children. This is now formally stated in an organization-wide policy statement.

- **Proprietary interest in the tested product (21 CFR 54.4(a)(3)(iii), 54.2(c))**

Relying on information available internally, Glaxo Wellcome has determined that no clinical investigator participating in the "covered study" has a proprietary interest in Trizivir (abacavir sulfate/lamivudine/zidovudine).

- **Significant equity interest in the sponsor of the covered study product (21 CFR 54.4(a)(3)(iv), 54.2(b))**

Relying on information obtained from the clinical investigators, Glaxo Wellcome has determined that NO clinical investigator participating in AZL10001 has indicated that he/she holds a significant equity interest in Glaxo Wellcome. A *Financial Interest in Glaxo Wellcome form* was returned by each participating Principal and Sub-Investigator. Specific information is located in Item 19 (Vol. 8, Page 239) of this application.

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- ☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigator	NDA 21-205: Trizivir (abacavir sulfate/lamivudine/zidovudine) Tablets Original New Drug Application	See Attached Listing

- ☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- ☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Lucy G. Martindale	Vice President and Director, R&D Finance
FIRM / ORGANIZATION	
Glaxo Wellcome Inc.	
SIGNATURE	DATE
<i>Lucy G Martindale</i>	NOV 17, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



RECORD OF TELEPHONE CONFERENCE

Date of Meeting: October 8, 1999

NDA: 21-205

Drug: Trizivir™ (abacavir sulfate/lamivudine/zidovudine) Tablets

Indication: Treatment of HIV-1 infection

Sponsor: Glaxo Wellcome Inc. (GW)

Type of Meeting: Pre-NDA CMC Telecon

Glaxo Wellcome Participants:

- Wayne Wood, B.S.
- John McCune, Ph.D.
- Jim Zisek, B.S., M.B.A.
- Martha Anne Moore, R.Ph.

FDA Participants:

Rao Kambhampati, Ph.D.
Stephen Miller, Ph.D.
John Martin, MD
Melissa Truffa, R.Ph.

Introduction:

Before DAVDP can comment on the review timeline for NDA 21-205, we propose that GW submit a rationale, if appropriate, for a priority vs. standard review.

Agenda Items

From the Pre-NDA Briefing Document, page 11

1. Dating of batch 8ZX032T will not allow its use for commercial purposes.
2. DAVDP requested that the CMC technical section of the NDA and the stability updates be submitted electronically as review aids. GW agreed to submit these data as Word or PDF files. DAVDP expressed a preference for WORD or Excel files if possible.
3. Impurities: DAVDP recommended that GW monitor the new impurity _____ in their stability batches and if it increases to a quantitative level of _____ it may need to be added to the specifications.

So far, GW has had no indications that the impurity will grow to _____ level when tablets are stored at room temperature, and therefore, has not conducted toxicity studies on the new impurity.

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Included in NDA 21-205 will be a report of all impurities (— will be reported as — and impurities — will be reported as actual values).

4. DAVDP requested that all specifications for each of the 3 drug substances be included with the NDA. GW agreed to submit this information as an appendix, which is acceptable.
5. DAVDP indicated that the currently used HPLC method involving UV detection at — is not specific enough for the identity testing of Trizivir Tablet and suggested that GW consider one of the following approaches: a) HPLC method using — b) an — method, and c) addition of a second method such as —. GW stated that they would evaluate — as a second method for the identity testing of Trizivir Tablet.

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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: October 18, 1999

DUE DATE: Not specified

OPDRA CONSULT #: 99-071

TO: Heidi M. Jolson, M.D.
Director, Division of Antiviral Drug Products
HFD-530

PRODUCT NAME: Trizivir™
(abacavir 300mg, lamivudine 150mg and
zidovudine 300mg tablets)


MANUFACTURER: Glaxo Wellcome, Inc.
Research Triangle Park, NC 27709


NDA #: 21-205

CASE REPORT NUMBER(S): Not applicable.

SUMMARY: In response to an October 18, 1999 consult from the Division of Antiviral Drug Products, (HFD-530), OPDRA conducted a review of the proposed proprietary name "Trizivir" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA believes that the use of the proprietary name "Trizivir" poses no significant safety risk and, therefore, has no objections to the use of this proprietary name. We have made a number of recommendations for labeling revisions to minimize the risk of potential medication errors with the use of this product.


Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173


Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

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Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 14, 2000

NDA NUMBER: 21-205

NAME OF DRUG: Trizivir™ (abacavir 300mg, lamivudine 150mg, zidovudine 300mg combination tablets)

NDA HOLDER: Glaxo Wellcome, Inc.
Research Triangle Park, NC 27709

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530) for assessment of the proprietary name Trizivir™ proposed by the sponsor.

The name Trizivir was submitted to the Labeling and Nomenclature Committee (LNC) on October 5, 1999. However, it is not clear from the available documentation what the LNC consensus was regarding this proprietary name.

Trizivir is a combination tablet indicated for the treatment of HIV-1 infection. The three active ingredients in this tablet are abacavir 300mg, lamivudine 150mg and zidovudine 300mg, all of which are currently marketed as individual products in the U.S. The usual adult dose of Trizivir is one tablet given twice daily.

II. SAFETY AND RISK ASSESSMENT

A. Product name search, product availability and dosing comparison, and focus group

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{iii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or

ⁱ MICROMEDEX Healthcare Intranet Series, 1999, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 1999).

ⁱⁱ American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

^{iv} Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug and Generic Drug Approvals 1998-1999, electronic online version of the FDA Orange Book.

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look alike to Trizivir™ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted*. A focus group discussion was conducted to review all findings from the searches.

Two product names were reviewed in the focus group that were thought to have some minimal potential for confusion: trazodone and Tri-Vi-Flor. Trazodone (Desyreℓ™) is an antidepressant supplied as 50, 100, 150, and 300-mg tablets, with a recommended usual adult daily dose between 150 and 600mg per day. Tri-Vi-Flor is a pediatric fluoride-containing multivitamin supplement supplied as chewable tablets which contain 1 mg fluoride and oral drops which contain 0.25 and 0.5 mg fluoride per mL. However, it was concluded that confusion of Trizivir with any of these drug product names in a clinical practice setting was unlikely, given the differences in dosage forms, intended patient populations, and available strengths.

B. Handwritten and verbal analysis of proposed name

A study was conducted within FDA employing a total of 46 health care professionals to evaluate potential errors in handwritten and verbal communications of the name Trizivir. This exercise was conducted in an attempt to simulate usual clinical practice settings. One of the following prescriptions was communicated per each study participant. Each reviewer was then requested to provide an interpretation of this prescription via email.

HANDWRITTEN INPATIENT ORDER (n=23)	VERBAL INPATIENT ORDER (n=23)
D/C Combivir Trizivir i b.i.d.	D/C Combivir Start Trizivir one tablet b.i.d.

Table 2: Verbal Prescriptions

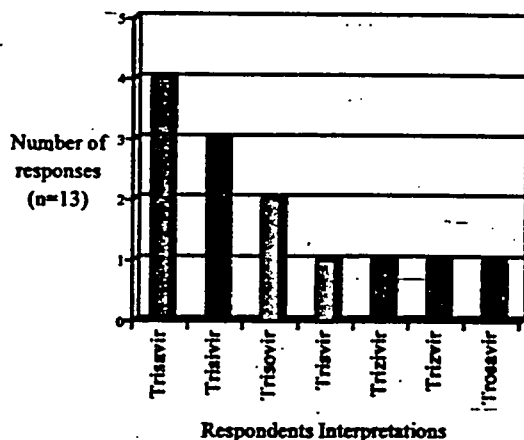
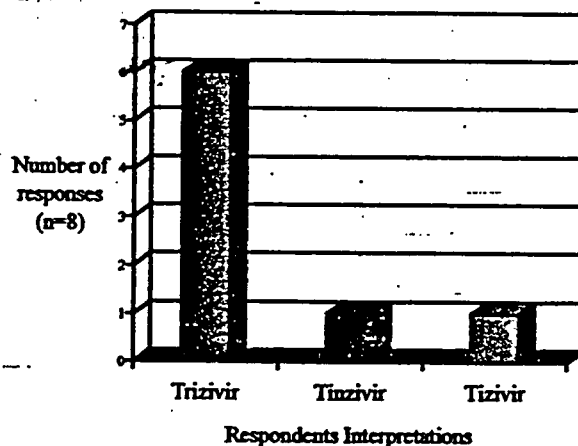


Table 3: Written Prescriptions



Results of this exercise are provided in Tables 2 and 3. A low response to these surveys occurred, which make these data difficult to interpret. This low response rate was presumed to be related to holiday absences among participants. We received responses from 13 of 23 (57%) surveyed with verbal prescriptions and 8 of 23 (35%) surveyed with written prescriptions. The majority of verbal respondents provided misspelled variations of the drug name but these responses generally were

* WWW location <http://www.uspto.gov/tmdb/index.html>

phonetic variations of the name. The majority of written prescription respondents provided the correct spelling of Trizivir (6 of 8, 75%).

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In reviewing the draft product package insert, patient Medication Guide, and product labeling (e.g., carton and container labels) for Trizivir, OPDRA has attempted to focus on safety issues relating to potential medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and medical officer.

We reviewed the draft product labeling for Trizivir and identified some labeling, packaging, and safety concerns.

A. CARTON and CONTAINER LABELING

1. We recommend that the _____ be deleted, as the presence of this information provides an unnecessary distraction in reading the product labels.
2. We recommend deletion of the statement _____ '21 CFR 201.1 h (1) sets forth various recommendations on the expression of relationship between a distributor, manufacturer, and/or labeler. The regulations do not allow others (e.g., licensors) to be included. This information appears in the draft package insert.

IV. DISCUSSION

In reviewing this proprietary name, two product names were identified that had some minimal similarity to Trizivir but were considered unlikely to be confused with this drug, particularly with consideration of dosage forms and usual dosing of these products. This finding was supported by written and verbal prescription surveys that were conducted, although a low response rate to these surveys occurred.

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V. RECOMMENDATIONS

- A. From a safety perspective, we believe that the use of the proprietary name "Trizivir" poses no significant safety risk and, therefore, we have no objections to use of this proprietary name.
- B. We recommend the above labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback on the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

151

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

151

1/17/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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cc: NDA 21-205
HFD-530; Division Files/Melissa Truffa, Project Manager
HFD-530; Heidi M. Jolson, Division Director
HFD-400; Debbie Boxwell, Safety Evaluator, DDREI, OPDRA
HFD-400; Carol Pamer, Safety Evaluator, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21205/000

Stamp: 17-DEC-1999 Regulatory Due: 17-JUN-2000

Applicant: GLAXO WELLCOME INC.

Priority: P

Action Goal:

Org Code: 530

District Goal: 17-APR-2000

Brand Name: TRIZIVIR (ABACAVIR
SULFATE/LAMIVUDINE/ZI

Established Name:

Generic Name: ABACAVIR
SULFATE/LAMIVUDINE/ZIDOVIDINE
3

Dosage Form: TAB (TABLET)

Strength: 300/150/300 MG PER TABL

FDA Contacts: M. TRUFFA (HFD-530)

R. KAMBHAMPATI (HFD-530)

S. MILLER (HFD-530)

301-827-2335 , Project Manager

301-827-2395 , Review Chemist

301-827-2392 , Team Leader

Overall Recommendation:

ACCEPTABLE on 02-JUN-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No:

AADA No:

Profile: CSN

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-MAR-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Responsibilities:

Establishment: 1033964

GLAXO INC

1011 NORTH ARENDELL AVE

ZEBULON, NC 27597

DMF No:

AADA No:

Profile: TCM

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-APR-2000

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE
MANUFACTURER
FINISHED DOSAGE
MANUFACTURER
FINISHED DOSAGE RELEASE
TESTER

Establishment: 1035048

GLAXO INC

5 MOORE DR

RESEARCH TRIANGLE PARK, NC 27

DMF No:

AADA No:

Profile: CTL

OAI Status: NONE

Responsibilities: FINISHED DOSAGE STABILITY
TESTERAPPEARS THIS WAY
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ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: OC RECOMMENDATION
Milestone Date: 06-JAN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 9610414 DMF No:
GLAXO WELLCOME OPERATIONS L AADA No:
DA1 5AH
DARTFORD, KENT, UK

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
Milestone Date: 02-JUN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: 9610419 DMF No:
GLAXOCHEM LTD AADA No:
DD10 8EA
MONTROSE ANGUS, SCOTLAND, UK

Profile: CSN OAI Status: NONE Responsibilities: DRUG SUBSTANCE
Last Milestone: OC RECOMMENDATION MANUFACTURER
Milestone Date: 10-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Record of FDA/Industry Meeting

Meeting Date: October 22, 1999
NDA Number: 21-205
Drug: Trizivir TM (abacavir/lamivudine/zidovudine) Tablets
Indication: Treatment of HIV-1 infection
Type of Meeting: Pre-NDA meeting
Sponsor: Glaxo Wellcome Inc.

FDA Attendees:

Heidi Jolson, M.D., M.P.H., Division Director, DAVDP
Debra Birnkrant, M.D., Deputy Director, Clinical, DAVDP
Walla Dempsey, Ph.D., Acting Deputy Director, Pre-Clinical, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
John Martin, M.D., Medical Officer, DAVDP
Prahbu Rajagopalan, Ph.D., Clinical Pharmacokinetics
Kellie Reynolds, Pharm.D., Clinical Pharmacokinetics Team Leader
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVDP
Lalji Mishra, Ph.D., Microbiology Reviewer, DAVDP
Jen DiQuanto, Clinical Pharmacokinetics Fellow
Melissa Truffa, R.Ph., Regulatory Project Manager, DAVDP

External Constituents:

Amy Keller, B.S., Project Leader, Trizivir
Deb Dawson, B.S., Clinical Development, Research Manager
Seth Hetherington, M.D., Senior Clinical Research Physician
Stephen LaFon, M.S., Clinical Development, Program Head
Lynn Smiley, M.D., Vice President Antivirals
Bill Spreen, Pharm D., Clinical Development, Senior Clinical Program Head
David Cocchetto, Ph.D., Regulatory Affairs
Randall Lanier, Ph.D., Virology
Jim Zisek, B.S., M.B.A., CMC Regulatory Affairs
Geoffrey Yuen, Pharm.D., Clinical Pharmacokineticist
Martha Anne Moore, R.Ph., Regulatory Affairs

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Background

On September 21, 1999 (SN037), Glaxo Wellcome (GW) submitted a request for a Pre-NDA meeting with Division of Antiviral Drug Products (DAVDP) along with a briefing document for their fixed dose combination tablet of abacavir sulfate, lamivudine, and zidovudine for the treatment of patients with HIV-1 infection. In addition to this briefing document, an agenda, questions/points of discussion, and a rationale for a priority review were provided to the Division on October 14, 1999 (SN044).

Points of Discussion/Agreements Reached

The following comments pertain to the sponsor's proposal for the format and content of NDA 21-205. Unless otherwise indicated, the proposals outlined in the September 21, 1999 briefing document are acceptable.

1. The submission of labels and cartons as color artwork rather than black and white draft labeling will be discussed with the Division of New Drug Chemistry at a later date for their comments and/or concurrence. In addition, DAVDP requested the label and carton components be submitted as soon as they are available so that they can be submitted for consult to the labeling and nomenclature group within OPDRA.
2. Proposals for the Chemistry, manufacturing, and controls (CMC) section of NDA 21-205 were discussed during an October 8, 1999 teleconference. The sponsor plans _____
3. The proposal for the human pharmacokinetics and bioavailability section of NDA 21-205 is acceptable. In addition, the sponsor has agreed to provide these data as ASCII files and data transport files to facilitate the review.
4. At the request of DAVDP, the sponsor agreed to _____
_____ ; from the combination tablet and the three individual products (Epivir®, Retrovir®, and Ziagen®).
5. At this time the proposal for the Safety Update is acceptable; however, the division may have additional comments at a future date.

The sponsor submitted the following questions/points of discussion on October 14, 1999. DAVDP responses are in bold font.

1. Based upon the preliminary results of the bioequivalence study AZLI0001, is this proposal for a bioequivalence NDA for TRIZIVIR acceptable by DAVDP? _____

The sponsor's proposal for a bioequivalence based NDA is acceptable to DAVDP.

2. GW has taken under consideration the Division's clinical comments of September 17, 1998. They would like to share their position/views regarding Trizivir and would like the review team's comments regarding these plans.

The NDA submission for the Trizivir Tablet will be a bioequivalence NDA with cross referencing to approved NDAs for Epivir®, Retrovir®, and Ziagen® for supportive clinical, non-clinical and drug substance data. GW intends to seek labeling for Trizivir for the treatment of patients with HIV infection where Trizivir may be used alone or in combination with other antiretroviral drugs (e.g., protease inhibitors, NNRTIs).

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GW believes that there is a significant patient population that will benefit from triple nucleoside therapy, either used alone or in combination with other antiretroviral therapies, to warrant introduction of an abacavir/lamivudine/zidovudine tablet. There are a variety of settings in which patient groups are expected to derive benefit from triple nucleoside therapy; Trizivir will potentially be used by some patients in the following populations:

- Therapy-naïve adults.
- Patients currently on or who will be prescribed a similar daily dosage of the single entities (ABC/3TC/ZDV or ABC/Combivir).
- Patients, who have virological suppression with 2 NRTIs plus a PI or NNRTI, but are unable to tolerate these regimens or find the pill burden unacceptable.
- Patients prescribed combination therapy that includes all 3 components as well as other antiretrovirals.

Current DHHS treatment guidelines support triple nucleoside therapy as an alternative option for the treatment of established HIV infection. Triple nucleoside therapy does fill a need for those patients whom, for whatever reason, elect to avoid the use of NNRTIs and/or PIs; GW is aware that this will not constitute the majority of patients on antiretroviral therapies.

- DAVDP does not approve combination treatment regimens for antiretrovirals.
- The label should reflect that this will be a combination product developed for dosing convenience, and not as a treatment regimen. The Division requested that GW submit a proposal for wording in the PRECAUTIONS section of Trizivir label that discusses the advantages and disadvantages associated with the use of this combination product. In addition, DAVDP recommended that the sponsor consult the Rifater™ product label for an example of a similar situation in which a combination product developed for convenience was approved.

3. GW wishes to work with DAVDP to position Trizivir in the most appropriate manner. The sponsor understands the Division's concerns that Trizivir, like all antiretroviral products, be promoted in a responsible manner. Therefore, GW seeks the Division's thoughts on the following labeling issues:

- As part of labeling, we propose _____

- Indications: GW proposes _____
- Description of Clinical Studies – As done previously at the time of initial approval of Combivir, GW would anticipate making the general statement _____
_____ There are several ways in which to handle this section of the label. As with Combivir,
_____ Our preference would be to include results from the following studies under the Description of Clinical Studies:
 - CNAAB3003 – 16 week results and
 - CNAAB3005 – 24 or 48 week results.

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In addition to the two studies listed above, DAVDP recommends that study CNAB3006 be included in the clinical trials section because it provides useful information that is applicable to a heavily pre-treated patient population. The sponsor can describe the results of this study in a few concise summary statements.

With regard to study CNAAB3005, the 24 and 48 week safety and efficacy data will be reviewed as a standard (10 month) efficacy supplement submitted to NDA 20-977 and NDA 20-978 for ZIAGEN tablets and oral solution. Any changes to the Ziagen label that result from the review of these data will be appropriately reflected in the labeling for Trizivir whether at the time of an action for NDA 21-205 or at a later date as a labeling supplement submitted to the Trizivir NDA. Please note that because of the anticipated dates of submission and differences in review timelines for the Trizivir NDA and the Ziagen 48 week supplement, data from the CNAAB3005 trial will not be considered for inclusion in the Trizivir label until after an action has been taken on the Ziagen supplement.

The sponsor noted that their preference was to submit both the 24 and 48 week data from 3005 to the NDAs for Ziagen in December 1999, which is acceptable to DAVDP.

4. As requested, the sponsor provided their rationale for review status for the triple tablet NDA. GW would like the review team's guidance on the acceptability of our proposal that the triple tablet NDA receive a priority review status. Does the team agree that the triple table NDA warrants a priority review timeline?

Our plans for the triple tablet include using tablets from our validation batches as part of our launch materials. In order to maximize product shelf life, manufacture of the tablets will coincide with the anticipated review timeline. If the NDA receives a priority review designation, validation batches will be made in March 2000. If the NDA receives a standard review designation, validation batches will be manufactured in July 2000.

Based on the sponsor's rationale that a one tablet vs. two or three tablets per day treatment regimen will enhance patient compliance, DAVDP has determined that this NDA should receive a priority review.

Other Discussions/Action Items

Signature, minutes preparer: _____ Date: _____

Attachments: Attendee List _____
Copy of sponsor's overheads _____

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NDA 21-205

January 7, 2000

GlaxoWellcome Inc.
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Moore:

We have received your new drug application (NDA) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Trizivir™ (abacavir sulfate/lamivudine/zidovudine) Tablets
Review Priority Classification: Priority (P)
Date of Application: December 16, 1999
Date of Receipt: December 17, 1999
Our Reference Number: NDA 21-205

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 15, 2000, in accordance with 21 CFR 314.101(a). If the application is filed the user fee goal date will be June 17, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at (<http://www.fda.gov/cder/pediatric>) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Melissa Truffa, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: February 29, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: John Martin, M.D., Medical Officer, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

The Division requests that the following be provided for our review, prior to taking an action on the Trizivir NDA:

1. Please provide a plan for determining and comparing rates of abacavir-associated hypersensitivity reaction and death in patients receiving Ziagen tablets vs. Trizivir tablets.
2. Please propose criteria for determining whether continued marketing of Trizivir is justified, in the event that the Trizivir NDA is approved, and abacavir hypersensitivity reaction and/or death occurs with a disproportionately greater frequency in Trizivir recipients vs. Ziagen.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Melissa M. Truffa, R.Ph.
Regulatory Health Manager, DAVDP
Division of Antiviral Drug Products

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 1, 2000
To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.
From: Melissa M. Truffa, R.Ph., DAVDP
Through: Therese Cvetkovich, M.D., Medical Team Leader, DAVDP
NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets
Subject: OPDRA consult.

The following comments are being conveyed on behalf of the Office of Postmarketing Drug Risk Assessment.

1. From a safety perspective, the use of the proprietary name "Trizivir" poses no significant safety risk and, therefore we have no objections to the use of this proprietary name.

The following comments pertain to the CARTON and CONTAINER labeling.

2. Please consider deleting the listing of U.S. Patent Numbers, as the presence of this information provides an unnecessary distraction in reading the product labels.
3. Please consider deleting the statement _____
21 CFR 201.1 h (1) sets forth various recommendations on the expression of the relationship between distributor, manufacturer, and/or labeler. The regulations do not allow others (e.g., licensors) to be included.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 1, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: Rao Kambhampati, Ph.D., Chemistry Reviewer, DAVDP
Stephen Miller, Ph.D., Chemistry Team Leader, DAVDP

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Subject: CMC comments.

Please address the following chemistry, manufacturing, and controls (CMC) comments and recommendations that are related to the NDA #21-205 for Trizivir™ (abacavir sulfate/lamivudine/zidovudine) tablets.

1. Please provide the current specifications for Ziagen® (abacavir sulfate, 300 mg), Epivir® (lamivudine, 150 mg), Retrovir® (zidovudine, 300 mg), and Combivir® (lamivudine/zidovudine, 150/300 mg) tablets.
2. The currently used reversed-phase HPLC method involving UV detection at _____ for the identification of abacavir, lamivudine, and zidovudine in Trizivir tablets is not specific enough to discriminate between compounds of closely related structures, therefore, please consider one of the following approaches:
 - a. Use UV/ _____ in the current HPLC method.
 - b. Add a second identity method such as normal-phase _____ to the current HPLC identity test.
 - c. Use specific methods such as _____ as a single identity test.
3. Since significant formation of a new impurity _____ was observed when tablets were stored for two months at 40°C/75%RH under exposed condition, we recommend that you include moisture content in the batch release and stability specifications until a significant amount of the stability data is generated.
4. Please include a test for microbial limits in the batch release and stability specifications or alternately, provide data that support the exclusion of this test in the batch release and stability specifications.

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5. Please provide a copy of the actual drawing for the _____ package and indicate its various components.
6. Since significant amounts of the following impurities, _____, and _____, were observed when tablets were stored for two months at 40°C/75%RH under exposed condition, we recommend you to test the stability samples for these impurities and report their contents.
7. In the stability protocol for the NDA lots, please include the moisture content test as a requirement instead of "For information only" until a significant amount of the stability data is generated.

The following are related to container/carton labeling:

8. In order to comply with 21 CFR 201.1 h (1), please delete the statement _____
9. Please make the established name more prominent by increasing the size and/or thickness of letters in "abacavir sulfate/lamivudine/zidovudine". If additional space is needed for this change, you may consider deleting the U.S. Patent Numbers from the container label.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Melissa M. Truffa, R.Ph.
Regulatory Project Manager, DAVDP
Division of Antiviral Drug Products

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GlaxoWellcome

March 16, 2000

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

DESK COPY

**Re: NDA 21-205; Trizivir™ (abacavir sulfate/lamivudine/zidovudine) Tablets
90-Day Safety Update**

Dear Dr. Jolson:

Reference is made to our Pre-NDA meeting on October 22, 1999 and a communication on December 9, 1999 between members of your Division and representatives of Glaxo Wellcome Inc. Reference is also made to the submission of New Drug Application (NDA) 21-205 to your Division on December 16, 1999. The purpose of this submission is to provide a safety update to the data submitted in the NDA in accordance with the regulations contained in 21 CFR 314.50 (5)(vi)(b).

As was agreed, we are providing a 3-month safety update for Trizivir NDA 21-205. The information contained in the update covers the time period from submission of the NDA (December 16, 1999) through March 1, 2000. Updated information is provided for Glaxo Wellcome sponsored studies (AZL30002, AZLF30002, AZL30003 and ESS40005) and collaborative studies (French ATU and Swiss Maintenance).

This submission is provided in duplicate; an additional four (4) desk copies are being sent directly to Ms. Truffa for use by the review team. If you have any questions regarding this submission, please contact me at (919) 483-9347. Thank you.

Sincerely,

Martha Anne A. Moore

Martha Anne A. Moore, R.Ph.
Project Director
Antiviral/Anti-Infective Regulatory Affairs

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Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 24, 2000

To: Martha Anne Moore, R.Ph.
Glaxo Wellcome Inc.

From: Melissa M. Truffa, R.Ph., DAVDP

Through: John Martin, M.D., Medical Officer, DAVDP
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

NDA: 21-205 Trizivir (abacavir sulfate/lamivudine/ zidovudine) Tablets

Subject: Proposal for alternate draft format for Trizivir Labeling.

As per our March 10, 2000 discussion, we propose that an alternate format for Trizivir labeling be drafted for consideration. In this alternate draft, we propose that key safety information as well as Trizivir-specific information be included.

For this alternate draft Trizivir label, we propose that you include the lines indicated below, or refer to the appropriate Ziagen and/or Combivir labels. The following line numberings refer to sections of the draft Trizivir label as submitted in the NDA, beginning on page 11.

Lines 1-44: include
Lines 45-72: refer
Lines 74-182: refer
Lines 184, 187-193: include
Lines 185-186, 194-220: refer
Lines 222-229: include
Lines 230-244: refer
Lines 245-250: include
Lines 251-259: refer
Line 260: omit
Lines 261-293: refer
Lines 294-301: include
Lines 301-347: refer
Lines 349-403: include
Lines 404-408: refer
Lines 409-434: include
Lines 435-503: refer
Lines 504-507: include

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Lines 508-539: refer
Lines 540-588: include
Lines 589-642: refer
Lines 644-670: include

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

cc:
Original NDA 21-205
Division File
HFD-530/CSO/Truffa

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